REMARKS

This Submission is responsive to the Office Action mailed September 26, 2007.

Claims 1 and 15 have been amended, and new claim 17 has been added. Support for the amendments to claim 1 and new claim 17 can be found throughout the specification and in particular at page 13, lines 1-4, 12-15 and 18-19, and page 14, lines 1-7. Support for the amendments to claim 15 can be found throughout the specification and in particular in the example at page 57-60. Claim 1 has also been amended to alter the definitions of R2 and R3.

REJECTION UNDER 35 USC 112, 1st PARAGRAPH, WRITTEN DESCRIPTION

At pages 2 and 3 of the Office Action, the Examiner rejected claims 1-7, 9, 15 and 16 under 35 USC 112, first paragraph as failing to comply with the written description requirement. In the present Office Action the Examiner alleged that there was insufficient written description of the invention because only a few heterocyclic rings are exemplified.

Applicants again traverse this rejection.

The present rejection was originally given to the claims in the first Office Action because the Examiner alleged that the specification does not contain a definition of heterocyclo and heteroaryls, heterocycloalkyl and alkylheteroaryl groups in the specification, and that in various places the claims recite forming a ring with N, O or S, but there is no definition as to which groups are encompassed by this in the specification. Applicants responded by pointing out the definitions of these groups in the specification. The definition of heterocycloalkyl and heterocycloalkanoyl can be found in the specification at page 13, lines 1-6 and page 11, lines 18-22. The definition of heteroaryl can be found in the specification at page 13, line 18 to page 14, line 7 (including the table). The definition of alkylheteroaryl can be found in the specification at page 13, line 18 to page 14, line 7 (including the table) and page 11, lines 18-22.

Applicants also responded to the Examiner's other concern that in various places the claims recite forming a ring with N, O or S, but there is no definition as to which groups are encompassed by this in the specification. Applicants pointed out that the specification adequately describes these groups. Substituents R5 and R8, R21 and R22, R24 and R25, and

R31 and R32, together with the N, can form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, and S. The number of carbons in the rings will depend on the identity of the substituents that combine to form the ring and the optional presence of another heteroatom. Persons skilled in the art will be able to determine which nitrogen-containing 4, 5, 6, 7 or 8 member rings can be formed from any two specified substituents.

In the present rejection, the Examiner alleged that the written description was inadequate because Applicants have not provided enough examples of various heterocyclic groups. The Examiner alleged that the generic definitions given in the specification and disclosure of three heterocycloalkyl rings, pyrrolidine, piperidine and morpholine was not commensurate to the scope of the claims, and Applicants have not reduced the invention to practice. The Examiner also alleged that a few examples have been given, but these are not commensurate to the fraction of the scope of Applicants' claims.

Applicants again respectfully submit that the specification provides sufficient written description of the claimed compounds to satisfy the requirements of section 112, first paragraph.

A description requirement issue can arise in a number of different circumstances where it must be determined whether the subject matter of a claim is supported in an application as filed. While a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. Consequently, rejection of an original claim for lack of written description should be rare. See MPEP 2163.03.

In order to satisfy the written description requirement of 112, first paragraph, the Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is claimed. *Vas Cath Inc. v. Mahurkur* 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Possession of the invention may shown in a variety of ways. One shows that one is "in possession" of the invention by such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention. *Lockwood*

v. American Airlines 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). The Guidelines for Examination of Patent Applications Under the 35 USC 112, ¶ , "Written Description" Requirement, Federal Register, vol. 66, pages 1099-1111, 2001, referred to in this response as the "Written Description Guidelines," state that an Applicants may show possession of an invention by an actual reduction to practice, by disclosure of drawings or structural formulae that are sufficiently detailed to show that Applicant was in possession of the invention, or any description of distinguishing or identifying characteristics sufficient to show that Applicant was in possession of the claimed invention. (Written Description Guidelines, page 1104, right column).

The Examiner's analysis of written description focuses on whether or not the Applicants have provided enough examples of ring systems or specific compounds to be a representative of the claims, and thus provide adequate written description of the claimed "genus." The Examiner's reliance on number of examples to determine compliance with the written description is misplaced. The case law has consistently held that Applicants can describe their invention by descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention. As stated in footnote 40 of the Written Description Guidelines,

> "In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406

Moreover, the portion of the Written Description Guidelines cited in the Office Action on page 9, has been misquoted. The relevant portion from page 1106 of the Written Description Guidelines states:

> "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above)."

The case law makes it clear that Applicants can satisfy the written description requirement, showing they were in possession of the invention, by such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention. There is no requirement that Applicants reduce the invention to practice, or provide any specific number of examples.

In the present application, Applicants are claiming certain fredericamycin derivatives. The compounds have been described using chemical formulae and description of possible values for the variable substituents in the formulae. The formulae and variable substituents are defined and discussed in the specification. Claim 1 has been amended to clarify the description of heterocycloalkyl and heteroaryl. The definition heterocycloalkyl in the specification is not limited to only three specific groups, as alleged by the Examiner. Page 13, lines 5-6 of the specification disclose at least nine different specific heteroclycloalkyl groups. Additionally, but not required, the specification contains over 150 examples of the claimed compounds, as well as data showing the antitumor activity of the compounds. Persons skilled in the art are left in no doubt that Applicants were in possession of the claimed compounds when the application was filed, as they can obtain any particular embodiment by simply selecting a value for each for the variable substituents of the formulae of the claimed compounds.

Applicants have shown that they are in possession of the invention by means of the chemical formulae set out in the specification, and the examples of specific embodiments of the claimed compounds. The specification thus provides adequate written description of claims 1-7, 9, 15 and 16, and new claim 17. Withdrawal of this section 112, first paragraph rejection is respectfully requested.

REJECTION UNDER 35 USC 112, 1st PARAGRAPH, ENABLEMENT

At pages 9-10 of the Office Action, the Examiner rejected claims 1-7, 9, 15 and 16 under 35 USC 112, first paragraph as not enabled for the reasons given in the previous Office Action. The Examiner alleged that the various R2, R3, and R5 groups with numerous variables and permutations makes the claim nebulous, and the art being so unpredictable, the Applicants need

to provide more. The Examiner also alleged that the specification does not enable the methods of treatment of tumors, parasites and other diseases.

Applicants again traverse this rejection. Claim 15, directed to methods of treating tumors using the compounds of claim 1, has been amended to limit the types of tumors to tumors selected from the group consisting of lung, breast, melanoma, renal, uterine and prostate tumors.

Applicants' remarks in the response filed July 10, 2007 are incorporated herein by reference.

According to the Examiner's comments in the present Office Action, the claims are directed to methods of treatment that are not enabled because of lack of data or guidance showing that the claimed compounds actually treat tumors or parasites. The Examiner's attention is again directed to MPEP 2107.03 "Special Considerations for Asserted Therapeutic or Pharmacological Utilities." Applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use as a matter of statistical certainty, nor does the applicant have to provide actual evidence of success in treating humans where such utility is asserted. Instead, all that is required is a reasonable correlation between the activity and the asserted use. Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound. If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

The specification at page 57, lines 1-4 in the section entitled "Biological activity against 12 cancer lines" and Table 7 presents data on the antitumor activity of the claimed compounds. The specification shows the averaged results of the efficacy of over twenty compounds of the invention in *in vitro* assays with twelve cancer cell lines, representing lung, breast, melanoma, renal, uterine, and prostate tumors. Adriamycin, cisplatin and fredericamycin, three known antitumor agents were also tested and the results shown in Table 7. In Table 7 the compounds of the invention are shown by a number in the left column that correlates with the example of the same number in the Example section beginning at page 58 of the specification. The claimed

compounds showed efficacy in the assays comparable to fredericamycin, and often the IC70 was lower than the IC70 of fredericamycin.

The compounds of claims 1-7 are derivatives of fredericamycin, a compound known in the art to have antitumor properties. The specification presents the same type of data as Yokoi et al., Misra and Kelly et al. to show antitumor properties of the compounds. Additionally, antitumor activity of the claimed compounds was compared with the activity of known antitumor agents, fredericamycin and adriamycin in the same assay. Fredericamycin derivatives in Yokoi et al. and Misra had both antitumor and antibacterial activity. Applicants have shown a reasonable correlation between the activity of the compounds and the asserted uses. The data presented in the specification is therefore sufficient to enable to persons skilled in the art to make and use the claimed invention throughout its scope for treatment of tumors and parasites.

The dosage of the compounds of the invention is shown at page 15, lines 5-7. A dose of the compound depends on various factors such as age, condition and weight of the patient, as well as the type of application. The daily dose of active ingredient is usually between 0.1 μg/kg and 1 g/kg orally. With the guidance in the specification persons skilled in the art can arrive at an effective amount of a compound of the invention without undue experimentation.

For the reasons discussed above, the specification enables claims 1-7, 9, 15 and 16 and new claim 17. Withdrawal of this section 112, first paragraph rejection is respectfully requested.

REJECTION UNDER 35 USC 103

At page 3 of the Office Action, the Examiner rejected claims 1-7, 9, 15 and 16 under 35 USC 103 as being *prima facie* obvious over U.S. patents 4,584,377 (Yokoi et al.); 4,673,678 (Misra) and 5,166,208 (Kelly et al.). The present Office Action does not mention Duan et al., Delgado et al. and Okimoto et al. which were cited in the rejection under section 103 in the previous Office Actions. In the present Office Action, the Examiner stated that Applicants' R definitions include all the various sugars and other groups and hence these groups would inherently help in making the compounds more soluble.

Applicants traverse this rejection. Claim 1 has been amended to alter the definitions of R2 and R3, and clarify the definitions of heterocycloalkyl and heteroaryl. New claim 17 has been added.

A *prima facie* case of obviousness requires the following: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP at 2143.

The three cited patents, Yokoi et al., Misra and Kelly et al. each disclose fredericamycin A derivatives, but do not disclose or suggest the compounds of claims 1-7 or new claim 17.

Kelly et al. discloses at column 17, lines 50-65 that the fredericamycin A derivatives therein can be mixed together with pharmaceutically acceptable carriers to prepare pharmaceutical compositions. Kelly et al. states that, in general, water, a suitable oil, isotonic saline, aqueous dextrose (glucose) and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. There is no suggestion or disclosure in Kelly et al. that sugars would make the fredericamycin A derivatives more soluble. Neither Yokoi et al. nor Misra disclose or suggest the use of sugars to make fredericamycin A derivatives more water soluble.

The fredericamycin derivatives of claims 1-7 and new claim 17, drugs of claim 9 and the methods of claims 15 and 16 are not obvious in view of the combined teachings of Yokoi et al., Misra, and Kelly et al. There is no disclosure or suggestion of the claimed compounds in the combined teachings of the cited references. Also, there is no disclosure or suggestion in the cited references, or the knowledge of persons skilled in the art, to modify fredericamycin derivatives with sugars to make them more soluble.

As stated in the specification, Applicants surprisingly found that the fredericamycin derivatives of claims 1-7, especially those derivatized in ring A, represent potent drugs. The Applicants' method of introducing groups in ring A semi-synthetically produces compounds having such substitutions in which the water solubility and/or biological effect, in comparison with fredericamycin, can be significantly increased.

The compounds of claims 1-8, drugs of claims 9-10 and the methods of claims 15 and 16 are not *prima facie* obvious in view of the combined teachings of Yokoi et al., Misra, Kelly et al. Duan et al., Delgado et al. and Okimoto et al.. A suggestion or motivation to combine the teachings of the cited references has not been shown, and the combined references do not teach or suggest any of the claimed compounds. Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 14528-00001-US.

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Respectfully submitted,

Electronic signature: /Liza D. Hohenschutz/
Liza D. Hohenschutz
Registration No.: 33,712
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant